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>> Welcome everyone. Thank you for joining us for the American Brain Tumor Association's webinar series thank you for participating in today's free webinar. Our webinar today will discuss, immunotherapy for brain tumors, resented by Dr. Ian Parney. Please note that all lines during the webinar today are muted, and if you have a question you would like to ask please type and submit it using the question box in the webinar control panel on the right-hand side of your screen. Dr. Parney will answer as many questions as possible at the end of the presentation. Tomorrow, you will receive an invitation to complete a brief feedback survey. I cannot stress enough how important it is for you to follow up with the survey. It is very short and just a few questions. We ask that you take a few minutes to fill it out. We want your comments about today's webinar so your feedback is very important to us. We are starting to plan for 2015 webinars if you can believe that. We are be recording today's app does webinar that will be posted to the ABT website shortly. It will be under the anytime learning section piece. You will also receive a link once our webinar is available. We will for a moment as we began our webinar recording.

>> The American Brain Tumor Association is pleased to welcome you back to our webinar series. I webinar today will discuss immunotherapy for brain tumors. My name is Jillann Demes. I am the senior program manager at the American brain tumor Association. I am delighted to introduce our speaker Dr. Ian Parney. Dr. Parney is a neurosurgeon and cancer researcher at the Mayo Clinic in Rochester, Minnesota. He received his M.D., the HT - - PhD and neurosurgeon all registry training at the University of Alberta and subsequent training and neurosurgical oncology at the University of California's San Francisco. His clinical practice and research interests are focused on malignant tumors. Thank you so much for joining us, Dr. Parney. You may now begin your presentation.

>> Thank you very much fat introduction is an honor and pleasure to be able to share this with the community today. What I am going to be talking about today is immunotherapy. Harnessing the immune system to fight brain tumors. As you heard, I am in neurosurgeon here at the Mayo Clinic in Rochester Minnesota. I do have a couple of disclosures to get out at the beginning. I had some grant support from the NIH, from the Ben and Catherine Ivy foundation. I am also a medical advisory board member for a genus Incorporated which is relevant to some of the information I will be sharing with you. I mean neurosurgeon. We are fairly good at neurosurgery these days. We can take a situation like this. This is a young man who was 23 that presented with seizures. He had this very large mass in his posterior right temporal lobe. You see this big horrible thing. And you can see the brain swelling out. We can use all of the tools that we normally have in surgery. We can use image guidance, MRI, the microscope. We can use all of these kind of adjuncts in surgery to convert the situation at the top with a big tumor, to a situation like we have a bottom with the same patient where we can get a resection of the Sumer and the brain is much less swollen. He did extremely well and went home on the second day after his surgery. If we can do that, why do we need to think about anything else for brain tumors for malignant gliomas in particular. The answer is these tumors although we can come out they can't have microscopic cells beyond what we can see that will come back at some point down the road. Even with an operation. There are other treatment options that are standard in oncology as I'm sure most of you know. We can think about surgery, we can think about radiation, we can think about chemotherapy. These treatments work. There is no question that particularly for glioblastomas if you are able to get the resection followed by radiation and chemotherapy you'll be able to do much better than if you do not have these treatments. By and

large the treatments are very well tolerated. But, still, his tumors tend to come back afterwards. So we need to have something better. There is a lot of people looking at a lot of different things. I have had an interest for many years in brain tumor immunotherapy. In trying to stimulate the immune system to attack tumors. What might this look like. Add a simple level if we are talking about a tumor vaccine, we might want to have something we can inject under the skin that would stimulate an immune response against the tumor stomach Lee. It would go back and left over with cells and a new - - aluminate them. The main system is designed to be specific so we hope this would just attack tumor cells and leave normal cells unharmed kind of like a silver bullet. That sounds great. Why do we just do all that? That's the question. How do we do that? That's what I am going to talk about today. Before we get into that I think we need to talk of it about immunology and general. I have titled this tide door slide immunology 101. I think it's worth asking just a simple question first. What exactly is the immune system? We all have a pretty good idea I think most folks can tell you what makes up the nervous system. The brain, spinal, - - court what makes up the cardiovascular system. Arteries and veins that would make sense. If I ask you what makes up the immune system, maybe it would be harder to answer and what part of your body is the immune system. There are some specific issues - - tissues and organs that are primarily responsible for things in the immune system. We're talking about lymph nodes, lymphatics which are the channels that dream lymph nodes. Spleen, your abdomen has a major immunological function. There are also a lot of other tissues and organs that you would not necessarily think of off the top of your head as being important in the main system have critical roles. The skin, the lungs, the liver, the gastrointestinal tract, the brain. All of these tissues have cells within them that their primary goal is as part of the immune system. When these tissues and organs are involved, but really what we are talking about the immune system we tend to talking - - be talking about white blood cells. I will be talking about it a lot of different white blood cells. Red blood cells are the ones that in your blood that Kerry oxygen. White blood cells are the ones that fight infection. They are the ones responsible for the human system. There are a lot of different white blood cells. There are cells called monocytes in the blood that we get out of the blood and into the tissues they become converted into something called macrophages. If you have an area where there has been different - - tissue damage you might have macrophages echoing to that area into a profitably - - debris and get rid of it. In the process of doing that they will also present aspects of that degree to the immune system to stimulate the immune system against things that they find there. There are other cells white blood cells called neutrophils eosinophils and other things. But really the most important one is a live the site. There are - - lymphocyte. There are T cells, and B cells and killer cells and a number of different types of lymphocytes. These are the ones that are really the workhorses of the human system. In particular, for some of the things that we are talking about today we are interested in stimulating killer T cells. That will go back and be activated against something in the tumor and then kill tumor cells. That is their job. So just to tell you in cartoon format this would be what it would look like in a cellular level. How you would get a T cells stimulated to attack a tumor cell. One of the things you have to have a something called an antigen presenting cell. I will come back and talk about what an antigen is in a minute. These are cells typically that are either macrophages or cells similar to macrophages and in particular there is a type of cell called a dendritic cell which is often thought of in the same family of cells as macrophages were. It is really good estimate leading T cells. The antigen presenting cell will have a bunch of the machinery and things that it needs to get a T cell activated. The T cells are very specific for these things. Antigens. Every T cell on the react against a certain antigen. What is new antigen? An antigen is a short piece of a protein that the body recognizes and specifically the immune system recognizes, as either foreign or dangerous. For example, if you have bacterial infection somewhere in the body. Bacteria produce proteins which are not normal in the body and the immune system will recognize those proteins and react against them. Similarly, if you have a tumor, the tumor will have proteins within it that are not normal or dangerous. The body in the

immune system will react against them by recognizing them. The ideas you have these antigen presenting cells present this antigen to a T cell that is specific for that antigen along with all of the other things needed to get it activated. This would look like something like this. Again you have your antigen presenting cell and maybe it went to an area where there was an infection or tumor and has picked up some of these antigens. It resents those antigens to in this case a killer T cell. That's a signal to stimulate and divide from that and then there is also other types of T cells like helpers that provides an signals. Then the killer T cell is going to pull a free and divide. We started with one and now you have many of these and then they will hold back through the body to the area where this infection is or where the tumor is and maybe there are some other cells here that are either infected or maybe the tumor cells that have all of the same antigens within the tumor, and these killer T cells are now effector cells will go back and kill the cells that have the antigens in there. The tumor cell will get killed by the T cell. If the immune system is so good, as you say it is and we all have immune system's why does anyone get a tumor? Because the immune system should recognize the tumor as abnormal and eradicated. The new system if it so good how can tumors grow? It's possible that our immune system does get rid of a lot of tumors that there may be microscopic cells all the time arising that have the potential to form tumors down the road, but maybe our immune system just recognizes them he gets rid of them before they ever come to anyone's attention. Of course we can get tumors. So how does that happen if the human system is so good? Well it comes down to this. Tumors are really good at turning the main system off. They can do this in a couple of different ways. One is that they can directly kill white blood cells that activated against tumor cells. So if you get a good stimulus here in the T cell and its activated to kill tumor cells, the tumor cells are still pretty good at killing those T cells before they can have the effect that you want. They also can work indirectly. Because with the tumor can do is convert normal white blood cells to a number of regulatory immune cells that turn the volume down on the Muses to. They make it - - immune system. They make hard to get immune system responses activated. The tumors have both direct and indirect ways to activate the human system. You end up with a system like this. In brain tumor patients what we want to see here is that you might have naïve T cells that get activated after coming into contact with hundred excels and appropriate antigens. The activated cells will go back and kill tumor cells, the problem is that we have a series of other cells. The tumor cells themselves, white blood cells, monocytes and then some of these other regulatory cells. Regulatory T cells but all of these populations will either inhibit the activation of these 10 lymphocytes - - T love the site. So far, this is what I would describe as a gosh cancer is bad top - - talk. It's really good at suppressing the main system. What I want to hear about is how we can do something better. How we can stimulate the immune system to do something. How can we do that? How can we stimulate the immune system to do its job? One way is that we can get a strong stimulus to get it going. One example of that that I will talk about in detail here is tumor vaccines. The idea here is that if it really does appear that we can generate a strong enough in your response and activate enough of the T cells to go back against the tumor, it can kind of overwhelmed a lot of the immunosuppression that is present. The other thing we can work at is to interrupt the tumor's ability to turn off in the immune system, so to give medication or other agents that will modulate the immune system. I will not talk about this as much I will come back and talk about it at the end. But this is actually a expanding area of research right now. So I wanted to talk about vaccines for tumors. You might be thinking will that's crazy talk. I know it vaccines are. They are those vaccines you get as a kid to prevent measles, mumps, rubella anachronistic. But whoever heard a vaccine for a tumor. Can you do that? Well yes you can do that. I want to go through a few ways that we can do this. What we're talking about here is therapeutic vaccines, not preventative vaccines. We're not trying to say that we would give every child when they start school a vaccine that would prevent them from developing a brain tumor later in life. But if we get to that point it might be something we could look out down the road. Right now what we're talking about is people who have a brain tumor who want to - - we want to give them a

vaccine to stimulate the immune system and attack whatever tumor cells they have left over. How do you do that? You need a few things. You need a source of tumor antigens. These proteins or parts of proteins that are abnormally dangerous and specific for the tumors. Tumors are chock-full of tumor antigens. You need a source of tumor antigens. You also need an effective way to get the immune system to respond to those antigens. In other words you need a mechanism to make a vaccine. There is a lot of different ways to do that. I will go through a few different approaches here. Probably the most widely tested type of tumor vaccine in general, and for brain tumors in particular, is something called the dendritic cell vaccine. You remember dendritic cells were those monocytes or macrophages like cells that are really good antigen presenting cells and really good at stimulating the immune system. What would it dendritic cell vaccine like? This is a good example. I will run through this. If you have someone with a brain tumor, you can take a sample of blood from that individual, and from their blood, you can purify a type of white blood cell called a monocyte. Then take those monocytes into the lab in a culture dish and under the appropriate conditions in the lab, you can convert those monocytes into dendritic cells. These very potent and powerful antigen presenting cells. So this can be than the basis of your vaccine. You of course also need as I said, tumor antigens. How you get those? The most Palm - - common way is this. Take the tumor itself that surgery, and in various ways basically top it up - - talk it up and get 10 - - antigens out from there. Basically take it straight from a tumor out of surgery. The idea then is that you combine these things the tumor antigen and the dendritic cell and you give them back usually just as an injected underneath the skin to the patient. What we hope with this is that it will take and represent naïve T cells and they will come in contact with the dendritic cells that have been primed with the tumor antigens that we got from a patient and that will generate activated T cells. We will go back and home to the tumor and eradicate tumor cells there. So dendritic cells have been around for quite a while. More than 10 years. In terms of brain tumors, there have been more than 16 clinical trials published. Ford didn't - - for dendritic cell vaccines. These have involved more than 10 different research groups across multiple countries and continents. And more than 350 patients have been reported. The results have been around for a while. We have a track record for this kind of thing. It is a little bit difficult to compare a lot of these studies. Because they are very different. There are large variations in the types of patients. Some studies only included great for theaters. - - Tumors some studies were new diagnosis. A lot of variations in the methods to grow these dendritic cells. Which it turns out is potentially really important. Lots of different measurements of immune responses. Almost every different study that you look at used a different way to measure and rim - - immune response. It is very difficult to compare. Nevertheless, it is some indication that some in - - something useful is going on. This study showed that survival was about 21 months which is if you think about what we would've expected for average survival over that time. Patients were beginning to be treated before that, so over the last 10 to 15 years, this is a higher survival than you would have - - or a longer survival average that you would've expected for most patients for glioblastoma is. See that the sense that maybe something useful is going on. There is at least one large multicenter phase clinical trial underway. There may be more but I know of at least one with Northwest which is being headed up by Dr. [Indiscernible] at UCLA. So did pretty vaccines have been a while. It's not really type vaccine. Another vaccine that you may hear about right now is a heat shock protein-based vaccine. So what are you Chuck proteins? Heat shock proteins are category of proteins that are present in every cell in the body. They normally act as what's called the molecular chaperone. They take other proteins are bits of proteins and they move them around the cell so the cell can use them in the appropriate manner. There is a particular type IV heat shock protein that is critical that moves antigens. It will be associated with a bunch of different tumor antigens there. So the idea is that you might take a chunk of tumor, taken out of surgery and isolate from not fresh tumor specimen, heat shock proteins with the year - - with their peptides and make that a vaccine that you can inject under the skin. There - - this works by using Hendrick cells - -

dendritic cells that have not been cultured in the lab. That is one less thing you have to do in the lab, but dendritic cells that are normally present in the skin. It turns out that a heat shock protein is really get it honing to hundred Excel. They bind to a specific receptor. There is right now, really the bulk of the work that has been done in heat shock protein peptide complex vaccines is the work of Dr. Andrew Parr set at Northwestern University. So it's through one of the collaborative groups there is now open a protocol a 071101. Patients would get either HSPPC 96 that the vaccine or Bevacizumab or the patients will get one of three of these. This will be for over 200 patients and it is now open at multiple centers across the United States. It's open at Mayo Clinic but also in another center as well. So this does a lot for the national Cancer institute. This is actually the largest cancer vaccine study ever. It's the largest vaccine trial of any type of solid tumor in the last decade. It's a cancer vaccine study conducted in combination with a [Indiscernible] which is quite novel. It is called [Indiscernible] so every individual patient's tumor is used to make tumor vaccines. So those didn't drink cell studies that I talked about and the heat shock protein vaccines that I have been talking about are what I would refer to as bulk antigen vaccine trials. So what do I mean by that? These are trials where the tumor antigens are obtained from the individual patient's tumor. In a lot of ways this is great, this is the ultimate in personalized medicine because if you have a tumor and we've made a vaccine from not tumor so it's very personalized. Certainly we want to do this. While there are some problems with bulk antigen approaches. Bulk antigens are a limited resource. You can only make as much vaccine as tumor tissue you have. Now I am a neurosurgeon and I make my living largely taking out breaking tumors - - brain tumors. Some of my patients are not always as keen on having another operation. I can respect that. Even if you do do an operation and get the tumor tissue, it's still ultimately a limited resource. You're only good to be able to give as much vaccine or make as much vaccine as you can get tumor tissue out. Eventually you will have to stop because you are running out of vaccine. That actually turns out to really matter. You tend to get a better response to any of these vaccines the more of the vaccine that you get. The other thing that is really a problem with these bulk antigen approaches, is that it's hard to test for specific antigens, to particular tumor antigens. Why is that the case? First of all, everybody's tumor is a little bit different. So if I am trying to design a clinical trial where I am going to test for tumor antigen responses, but patient A tumor antigens are different from patient B tumor antigens it becomes problematic to do that. I can't really design anything that will accommodate that. So why does that matter? It does because of this. We all want to see this. Here's a guy hitting a pitch out of the park. He is a home run. What a mean by that is we all want to see with our vaccine clinical trials that we have had a home run. We have had a clear unequivocal benefit to patients in terms of stimulating immune response and survival afterward. The problem with all of these studies is that it really hasn't happened yet. We see things that make us think that there are probably some benefit. Cobbett hasn't been home run like this where we can unequivocally say we got it. With that, the National Cancer Institute has turned around and said we understand why you want use antigens and its personalized medicine and that's great, but until you start showing us that you're getting some home runs, we really want you to test specific antigen responses. At least that way, we can decide if we have stimulated amine response - - and immune response. You can compare much better from study to study looking at different approaches if you are testing for specific tumor antigens. So people have done that and what did that and said well we are not going to do these bulk antigen approaches we're going to do other vaccines that are directed at particular tumor antigens. Probably one of the most developed of these approaches is this CDX 110. This is a vaccine that is a module. There are no cells are proteins, just a little bit of a portion of a protein from a particular tumor antigen. EGFR VIII. EGFR's immune protein that is only present in tumor cells. It is present in a number of brain tumor patients where this particular receptors activated all the time. You can make a vaccine but it is just purely directed against this one antigen. Does not involve any cells it just involves the molecules in a portion of that antigen that test a response. And John Sampson at Duke

University and Amy Heinberg are at Anderson have really done a fantastic job with this. This is some of their data from a clinical trial looking at patients with glioblastomas were treated with the vaccine. Looking at their survival over time and compared to patients that did not get the vaccine. This was not a randomized study. It's not like these patients were randomly chosen. These are the patients that one ought to the clinical trial. These are historic control patients. They did a pretty good job especially of matching the control patients to the patients in the clinical trial. It's a reasonable comparison, but it's not like it's a random study. You have to take it with a little bit of a grain of salt. It does look like there is a clinical benefit to this faxing. In terms of increasing survival. There are some problems with this kind of approach. Whether it's with this vaccine or others. First of all, they can to be for highly selected patients and specifically in that study, it was only for patients who had a GCR. That is not always possible to get patients depending on where the tumor is. Obviously it is only going to be an option for patients whose tumor expresses these things. Not every patient with Wale Bustamante is express this. If you are conservative probably only about 20% of this have expressions of this. The other kind of problem with vaccine that target this - - specific antigen. What I mean by immuno editing. If you are a tumor and your cells are expressing a lot of protein like EGFR three. The first thing the tumor is going to do is stop expressing it. And use other mechanisms to continue to grow in its absence. That is really exactly what happens in the study. So all of the patients enrolled in the study had tumors that were positive for EGFR V3 that was a requirement before they got the vaccination. Although there clearly seem to be some prolonged survival in patients that got the sex scene, most patients eventually have the tumor recur in a subset of those went on to have another surgery when the tumor record. When they looked at the EGFR VIII in the tumors that recurred most of them had actually lost the expression of this protein when they return. On one hand there's an immunologist who is excited because he said we generated and immune response, but for patients, this is so great because it just as well the tumor has escaped by doing this and we want to avoid that. What would maybe be an ideal antigen source for a tumor vaccine? You would want something that maybe combines the best features of both bulk antigen, and specific antigen approaches. I'd like to have something that can take many tumor antigens much more than just one or two because then it will be very hard for the tumor to just stop expressing all of those antigens. I'd like something that would allow antigen specific immune response testing. This week I can say did I generate or did we generate with our vaccine the immune response we said we wanted to generate. I want something that is widely available what does not require fresh to chew because that tissue is just often not available. So to that end, we have opened up at Mayo Clinic, this trial on the 1272. We think this has a better source for tumor antigens, we think that we actually have better dendritic cells than we have had in the past. I think we have better immunological monitoring that we have had in the past with a lot of vaccines. So I better source for tumor antigens when I mean by that? What we have done in this case rather than using patient's individual tumors as the source of the tumor antigens, we have grown under good manufacturing practices conditions. That is the clinical grade lab so this is a lab where people were spacesuits and it is very highly regulated, so in that scenario we have created a library of cell cultures from other patients with glioblastoma is that we respected and we have these cultures growing indefinitely and culture that we can use as a renewable source antigen. Now we have looked at expression of a number of common tumor antigens. That's what all of these are. You can see that some of these cells express some of the antigens cause some of them express all of the antigens. There is quite a bit of variation from line to line. But the point is, we have a defined antigen source that is renewable, we can use, to make a vaccine for anyone. It is not like this vaccine only includes these antigens. We assume that the cell culture is that we generated have many abnormal proteins that are potentially available to the immune system to respond against. So it will reduce the chance of there being significant immuno editing. But yet at the same time it will be renewable so that we can keep giving vaccines for a longer period of time, and we know at least some of the antigens that are present so we can test for

specific antigen responses after the vaccine. So I think we have a better way of making dendritic cells. What I mean by that? It turns out how you make dendritic cells, you culture them in the lab from the white blood cells called monocytes really matters. What you want to get at the end of your process of making the dendritic cells are mature dendritic cells. Because if you don't do this right, you can end up with immature dendritic cells and while mature dendritic cells stimulate the immune system immature ones inhibit the immune system. One marker for mature dendritic cells is a protein called CD 83 and its present on the surface of dendritic cells. If you look at the black circle tear this is healthy donor circles or the red triangles are patients with glioblastoma Scott if you use a standard technique to make dendritic cells, this is been optimized with normal healthy donor blood samples. You can get a lot of mature tendered excels. This is what you want. The problem is, the glioblastoma patients their blood is not normal. There monocytes are not normal and they include a number of these regulatory cells that suppress immune responses in turn them down. If use the same technique that works well with really healthy normal donors and glioblastoma patients you get a whole lot of immature dendritic cells which are probably actually counterproductive. This work represents work from one of my colleagues here Dr. Alan Dietz. What he did was really smart and he went through a whole series of different techniques to culture dendritic cells with glioblastoma patients and that's how he came up with this technique. We call it the DC opt for technique. We're finally getting numbers of mature tendered excels that are comparable to what we would get a normal donors. So the DC opt 4 technique that we used to make dendritic cells. I also think we have better immunological monitoring and this gets back to being able to test the antigen specific responses, not only that, we have developed a simple method to independently determine expression of over 120 and your monocle's - - Monica - - molecules. This is actually been really powerful. Again it is Alan Dietz my collaborator, they used this profile. In this case it was only looking at 50 markers. This is a complex picture I know but I will try to walk you through this. Essentially what you're seeing on this access here. These are different immune cells are white light cell subsets. If you have a blue bar it means you have fewer of them. If you have a Graybar is an average number if you have a red bar it means you have more of them. There is actually three populations of people represented here. These in the center that will green, so all the way along here. These are normal healthy volunteers. This is what normal patients what their blood looks like when you look at the immune system. This population appear, and this population down here, these are both patients with glioblastoma's. What is very interesting here is you can see that these are actually different populations. There are three distinct populations, the normal donors, and glioblastoma patients here and here. These glioblastoma patients tend to have more of these cells. These are red and that means there was more of them, and these are the regulatory suppressor cells. So cells that inhibit the immune system were as these glioblastoma cells don't the other thing that has been very exciting is that these patients the one that had some evidence that they responded to the vaccine. Whereas these patients did not. This blood test was done based on blood sample that was taken before they got vaccinated. This is very exciting. We're trying to reproduce is now the second study in our ongoing clinical trial but the ideas that we might be able to identify what patients are going to respond to the vaccine, before we give it an these patients will have maybe some benefit or it may not be as beneficial for these over here. Then we can move on to others studies - - other studies for these patients. The other thing - - I will skip over the slide. But the other thing with this is that we can look at this in different ways. This is a healthy volunteer, much of these immune cell populations, this is a glioblastoma patient had a lot of these immuno suppressive site cells. This is the first patient in our vaccine study here. That and the 1272 that I was talking about. Thankfully he looks more like a healthy patient so he is hoping someone that will be responding to the vaccine. In the same patient, we are able to test for specific antigen responses. Again it is very exciting because we know what were vaccinated with and we are able to detect that. This population of cells here is the number of killer T cells that are specific for this tumor antigen. The GP 100. This is just a negative control

where you don't see any of those. You can see that in this patient most 1% of the killer T cells have been activated against this tumor antigen. That is really exciting. 1% may not sound like a lot but if you think of all the T cells we have we have activated at least 1% against this one antigen. That is pretty hopeful and promising that we will be generating an immune response that could be helpful for people. So this study is ongoing our recruitment is a little bit slow because the FDA has required us to go slow for the first three patients to make sure there are not complications. There have not been so far which is good. It is in combination with surgery, radiation, and chemotherapy. After the patients get the vaccine up until the cycle and then they get the vaccine alone. What about those patients with an unfavorable immune status. Our pulmonary data suggested that maybe some patients just don't respond to the vaccine. Can we identify those patients by in a major logical screening? We want to do something for patients and not coated gory as well. I think the key thing as time goes on is that we will be using a lot of these immuno modulating therapies plus or minus a vaccine. These are therapies that are designed to reduce the tumor's ability to inhibit the immune system. There's an old fashion type of doing this, called surgery. If we take out the bulk of the tumor there is a whole lot less of it there to inhibit the immune system so that is something that is important. There is a whole bunch of what I described as newfangled ones which I am not really going to talk about today but are increasingly important immune checkpoint blockade. So there's a medication called Ipilimumab which calls for a blocking of a blockade of [Indiscernible] people are beginning to look at that and glioblastoma's as well. There's another immune checkpoint called the PD-one PD-1/PD-L1 that are coming into clinical trials. So we're hoping that this is something that we may be able to utilize to help patients with more unfavorable immune status become favorable so that they might respond to that. So just to conclude with that I would say immunotherapy is a promising experimental approach to brain tumor treatment. Most commonly, this involves therapeutic vaccines combined with standard treatments. In the near future, I think immune modulating agents will also be available in clinical trials. I just want to acknowledge a number of people that I work with here and elsewhere US contributed to this in my lab and Dr. Dietz's lab in the Mayo Brain SPORE group and the University of Minnesota. And I'll stop there and would be happy to answer questions.

>> Thank you, so much. That was amazing. I hope everyone learned as much as I did from that. It is an exciting field that is coming up and it is amazing what you can do with all of that. It would be exciting even to come back together in a year and see what has changed with immunotherapy. So we do have some time for some questions. I will just remind you that if you do have a question that you can type it and submitted using the question box in a webinar control panel on the right side of your screen. We will start and we will see how many we can get to. Someone is asking about how long does the anti-PD 1K show to take results. She is also wondering whether trials planned and brain tumors combining vaccines in the anti-Petey one, or the PDL one.

>> I think that's an excellent question and I will just repeat it. So the person is asking about a particular antibody. NK 3475 that is directed against one of these immune checkpoint blockade. Against PD-one specifically. I think there were two questions in there. How long does it take to have the effect and will this be combined with vaccines in the future? So how long does it take to have an effect? First of all I would say the use of these immune checkpoint blockades in brain tumor patients is really in its infancy. There are a number of clinical trials that are just beginning to get going and may be this person is under treatment right now which would be great. But I don't know that we have a really great answer to how long it takes to work. What I can say is that based on other tumor types were people have been treated with these PD-1 specifically. What most commonly happens is the coffee just look at the imaging, the tumor is actually looking like it gets bigger first for a few weeks or even a few months. Then they begin to shrink after that. The thought is is that getting bigger may not actually be the tumor growing it may be the inflammatory response against the tumor that makes it look like it's getting bigger. That sort of shrinks down afterward. Time course for that at least in other

types of cancers in particularly in melanomas is measured over weeks to a few months. And another question was when will these, or will they be combined with vaccines? Absolutely. These will be combined with vaccines in the interest is very high. I think we probably need to get a little bit more data, little bit more information about how brain tumor patients respond to treatment with these inhibitors by themselves first. So that we can have our baseline and then probably we will be looking at combining these with vaccines down the road. I would imagine probably within a year or so.

>> That would be great. Some is wondering about [Indiscernible] which is something that here we take questions then the static tumors as well as primary brain tumor so if they have a metastatic tumor can this type of therapy work on metastatic cancer?

>> Yes. I would say there is potential for that. All of these immunotherapies are experimental now. Whether someone with metastatic rain tumor - - brain tumor is going to be eligible for clinical trial would really depend on the specific clinical trial. I have to say unfortunately, a lot of the clinical trials for vaccines for the immune checkpoint inhibitors for a lot of a lot there are systemic tumors like melanoma or lung cancer breast cancer. They will often specifically exclude patients who have brain metastases less those metastases had been definitively dealt with by either surgery or radiation along those lines. I am not aware of anyone doing clinical trials and making vaccines based on brain metastases themselves. But, it's something that it certainly could be done and eventually something that we have interest in as well.

>> We will try to fit one or two more in. Are there any immunotherapy dendritic cell vaccines in the United States that do not require inclusion of the brain tumor cells organized to be taken from surgery?

>> Yes. There is the study that we have open here at Mayo Clinic. NC 1272 which we use as a tumor antigen source. These established clinical grade cell lines from other patients. We don't need to get brain tumor tissue from each individual patient to make the vaccine. So yes. We have a study like that that is open. There may be others around the country as well. And they may be opened by him not aware of them. Our own study with the first three patients we have to do make sure that they do well. We will be getting there soon probably in about three months.

>> Wonderful. If anyone is interested in how to search for clinical trials they are welcome to call us at the main - - and American Brain Tumor Association. Our number is one 800-886-2282. We have partnered with emerging med and trial connect and we can connect you with that service to look for clinical trials in this category and other categories to see that you can find the best one that will work for you or your family member. A lot of people are asking questions about that. Like Hattaway start to find a physician as a social worker I was talk about contact your insurance company, but it is also a matter of what other treatments you've had right?

>> Right every individual clinical trial has specific inclusion and exclusion criteria, and not everybody will be eligible for every study. But there are many studies out there, not just immunotherapy studies but many different treatments and one of the other things that you you can look at is clinical trials you can look@isclinicaltrials.gov online and look up brain tumors and I can find a lot of different trials that are open at various places across the country.

>> That's correct. Definitely multiple sources to get your information, and we are always happy to help you after this presentation if you have any questions just as a reminder the presentation does post to our anytime learning question - - sorry anytime learning section of our website trend 20 so you can listen to this over and over if you have time to listen to questions. Because it is a new subject and confusing subject, so it is always there. We ought the top of the hour so I want to respect everyone's time and end on time, so we are going to say that that is all the questions we

have time for. I would also like to let you know or more information on immunotherapy it is available at her website at Www.abta.org or we can value information. Once again Dr. Parney thank you again so much, you are a walking wealth of information. We just really appreciate they took the time totally today, but in the weeks and the months that we have been working with you to put this together for us. Thank you again.

>> It's an honor and a pleasure. Thank you for the opportunity.

>> I am going to pause for just a second and we are going to stop the webinar recording, and then I will do a little bit more housekeeping, and go from there. So we invite you to check back to our website which is Www.abta.org . We do have are more webinars coming. Our next to webinars is next Tuesday, July 15 it is from 1 to 2 PM on pediatric what - - low-grade gliomas. That will be presented by Dr. heater Manley he is a pediatric oncologist at Dana-Farber and he is also an instructor in pediatrics at Harvard Medical School. He will discuss the advances in treatment and long-term survival of children treated for low-grade gliomas which is the most common pediatric brain tumor. Then on Wednesday, Then on Wednesday, August 6, 2014 from 2 to 3 central time again is demystifying allocative care. There is so much confusion about allocative care versus hospice quality of care starts at the date of diagnosis is symptom and whole body management of pain. Please don't think that it has anything to do with hospice from the beginning. Don't be afraid to ask for a palliative care team to help you out with your pain issues and your symptoms of fatigue, or anything. That is my bandwagon speech on palliative care. I would like to join Michael Chan M.D. assistant professor at the concrete pensive - - copperheads of cancer center as he explains what you can expect I adding this treatment modality to your care. In the meantime I would, again, encourage you to call her 800 number and talk to our social workers and really learn more about what palliative care can do for your life and ease the stress and burden of the caregiver. Last but not least, we are having our annual brain tumor conference July 25 and 26 in Chicago. We are the longest running national brain tumor conference in the country. With leading experts in the brain tumor community that come to Chicago to speak to patients. They give up their weekend and they talk to you about topics such as diet, immunotherapy, nutrition, integrative medicine, the list goes on and on and on. It is a wonderful price for two days for $100 all your meals included, all the presenters, all the handouts, everything you can possibly need and learn you will get from this conference. Just go to brain tumor conference.org or call us at 800-80-86-2282 and register today. While one a miss this. If you thought this webinar was good and this is just one hour, you will have two days of these types of presentations. I would love to see you there. This concludes our webinar, thank you for joining us, and please be sure to complete the webinar series survey you will receive shortly after the session. You may now disconnect.

>> [Event Concluded]